

MALT lymphoma: a paradigm of NF- κ B dysregulation

Ming-Qing Du

Division of Molecular Histopathology, Department of Pathology,
University of Cambridge, Cambridge, UK

Key words: MALT lymphoma, NF- κ B, Immunological drive, Genetic abnormalities

Correspondence to
Professor Ming-Qing Du,
Division of Molecular Histopathology,
Department of Pathology
University of Cambridge
Box 231, Level 3, Lab Block
Addenbrooke's Hospital,
Hills Road
Cambridge, CB2 2QQ
United Kingdom

Tel: +44 (0)1223 767092
Fax: +44 (0)1223 586670
Email: mqd20@cam.ac.uk

The author declares that there are no conflicts of interest.

Abstract

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) invariably arises from a background of **chronic microbial infection and/or autoimmune disorder** at diverse mucosal sites. **The prolonged chronic infection and/or autoimmunity generate active immune and inflammatory responses that provide a setting for evolution and development of autoreactive B-cells, their expansion and eventual malignant transformation following acquisition of genetic changes.** The immune responses also play a critical role in sustaining the growth and survival of the transformed cells as shown by complete regression of a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin following anti-microbial treatment. B-cell receptor engagement by auto-antigen as well as T-cell help including both cognate interaction and bystander help via soluble ligands such as CD40L and BAFF are thought to underpin the immunological drive in the lymphoma development through activation of the **canonical and non-canonical NF- κ B pathway respectively.** Similarly, the three MALT lymphoma associated chromosome translocations, namely $t(14;18)(q32;q21)/IGH-MALT1$, $t(1;14)(p22;q32)/BCL10-IGH$, and $t(11;18)(q21;q21)/BIRC3 (API2)-MALT1$, are also capable of activating both canonical and non-canonical NF- κ B pathways. Furthermore, *TNFAIP3* (A20) inactivation by deletion and/or mutation abolishes the auto-negative feedback to several signalling including BCR and TLR, which connect to the canonical NF- κ B activation pathway. Thus, there is a considerable overlap in the molecular pathways dysregulated by immunological drive and somatic genetic changes, **strongly arguing for their oncogenic cooperation in the development of MALT lymphoma.**

Nuclear factor (NF)- κ B is a family of dimeric transcription factors critical for both innate and adaptive immunities. In response to stimulation of a wide range of surface receptors, NF- κ B orchestrates gene expression and governs a variety of biological processes important for the development, maturation and function of immune cells. There are five NF- κ B subunits including RelA (p65), RelB, c-Rel, NF- κ B1 (p50 and its precursor p105) and NF- κ B2 (p52 and its precursor p100). They form various hetero or homodimers, but are kept inactive in the cytoplasm by their inhibitor (I κ B α , I κ B β and I κ B ϵ) or in its dormant precursor form. In response to surface receptor signalling, the quiescent NF- κ B dimer is activated, and permitted for nuclear translocation and transcriptional function. NF- κ B activation is mediated via two common signalling pathways, namely canonical and non-canonical NF- κ B pathway, and this is a transient and highly regulated process in response to extracellular signals under a physiological condition. Below highlights the key steps relevant to this review and for details on NF- κ B signalling please refer to other reviews [1-4].

1. NF- κ B activation pathway

Canonical NF- κ B pathway. This involves I κ B phosphorylation by the I κ B kinase (IKK) complex, triggering its K48-linked polyubiquitination and subsequent degradation by proteasome. As a result, NF- κ B dimers are released and their nuclear localisation signal exposed, thus enabling their nuclear translocation and transcriptional activities [Figure 1].

Canonical NF- κ B pathway is activated by stimulation of several surface receptors such as B-cell receptor (BCR), Toll-like receptor (TLR), interleukin 1 receptor (IL1R) and tumour necrosis factor receptor (TNFR). These receptor stimulations initiate various signalling cascades that involve distinct adaptor molecules, but converge on the canonical NF- κ B activation pathway. For example, BCR engagement triggers receptor aggregation, promoting tyrosine phosphorylation of CD79A (Ig α) and CD79B (Ig β) ITAM (immunoreceptor tyrosine-based activation motif), and recruitment of spleen tyrosine kinase (SYK). SYK activation then emanates multiple signalling cascades that connect to the canonical NF- κ B, PI3K-AKT and RAS-ERK activation pathways [1,2]. Through the Bruton's tyrosine kinase (BTK) and protein kinase C (PKC) β signalling cascade, the scaffolding adaptor CARD11 (CARMA1) is recruited, undergoes conformational changes and is able to interact with BCL10 and promote its polymerisation and filament formation, subsequent assembly of the CARD11/BCL10/MALT1 (CBM) signalosome complex [5-7]. The CBM complex further recruits TNF receptor associated factor-6 (TRAF6), transforming growth factor β activating kinase-1 (TAK1) and TAK binding protein-2 (TAB 2), which activates the IKK complex and culminates the activation of canonical NF- κ B pathway [5,8,9]. Similarly, TLR (or IL1R) engagement triggers its dimerisation and conformational change in its Toll/IL-1R homologous (TIR) domain, which results in recruitment of MYD88, Interleukin-1 receptor-associated kinase-4 (IRAK4) and IRAK1, forming the Myddosome complex [Figure 1]. The Myddosome complex then recruits TRAF6, TAK1 and TAB2, subsequently leading to activation of the IKK complex and canonical NF- κ B pathway [3,4].

The canonical NF- κ B activation pathway is also tightly modulated by several negative regulators including TNF α inducible protein 3 (TNFAIP3, also known as A20), I κ B α and CYLD (cylindromatosis) to ensure appropriate level and length of NF- κ B activation [Figure 1] [10,11]. I κ B α and TNFAIP3 are the transcriptional targets of NF- κ B, and their expression following NF- κ B activation could serve as an auto-negative feedback. TNFAIP3 can inactivate a number of NF- κ B signalling molecules including receptor-interacting protein-1/2 (RIP1/2), ubiquitin-conjugating enzyme 13 (Ubc13) and IKK γ (also known as NF- κ B essential modulator, NEMO), thus negatively regulating the signalling of several surface receptors including BCR, TNFR, TLR and IL1 β R [12-14].

Non-canonical NF- κ B pathway: This involves successive activation of the NF- κ B inducible kinase (NIK) and IKK α [Figure 1]. The activated IKK α phosphorylates NF- κ B2 (p100) and triggers its partial proteolysis, and this generates a functional active form p52, which is permitted, together with RelB, for nuclear translocation

and transcriptional function. The signalling from CD40, B cell activating factor receptor (BAFFR), TNFRSF13B (also known as TACI) and lymphotoxin β receptor (LT β R) primarily activates the non-canonical NF- κ B pathway. The non-canonical NF- κ B pathway is negatively regulated by TRAF3, apoptosis inhibitor-1/2 (API1/2) and TRAF2, which control the turnover of NIK by targeting it for ubiquitin mediated degradation by proteasome [15].

In view of the diverse signalling that trigger NF- κ B activation and its multiple functional roles in both innate and adaptive immunities, it is not surprising that NF- κ B dysregulation is implicated in a wide range of lymphomas including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), activated B-cell like diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, Hodgkin's lymphoma and multiple myeloma [16,17]. Among these, MALT lymphoma provides a unique model to appreciate the role of various immunological stimulations and genetic changes, and their oncogenic cooperation in lymphoma pathogenesis.

2. MALT lymphoma is causatively linked to chronic inflammation

MALT lymphoma may occur at diverse anatomic sites, but always at those that are devoid of any native organised lymphoid tissue. However, such organised lymphoid tissue can be acquired following a prolonged chronic microbial infection or autoimmune disorder, and it has been proposed that MALT lymphoma originates from the marginal zone B-cells of the acquired MALT as suggested by their immunophenotype and preferential marginal zone localization [18]. Although not yet fully characterised, MALT lymphoma at several sites is associated with distinct aetiological factors. For example, the vast majority of gastric MALT lymphomas develop from a background of chronic gastric *Helicobacter pylori* infection, while those from the skin and ocular adnexa, and immunoproliferative small intestine disease are variably associated with chronic infection of *Borrelia burgdorferi* [19-24], *Chlamydia psittaci* [25-28], and *Campylobacter jejuni* [29] respectively. Furthermore, MALT lymphoma of the salivary gland and thyroid are commonly derived from a background of lymphoepithelial sialadenitis and Hashimoto thyroiditis respectively [30,31]. For detailed association between etiological factors and MALT lymphoma, please refer to excellent recent review [32].

Despite association with different aetiological factors, the development of MALT lymphoma may follow a similar multistep process (Figure 2). The prolonged chronic microbial infection or autoimmunity generates immune and inflammatory responses that maintain a population of dynamic B-cells in a microenvironment at an increased risk of genomic damage. B-cells attaining certain immunological properties and/or genetic changes may gain growth advantage and undergo clonal expansion, eventually emerge as a transformed clone on rare occasions. Presence of minor clonal B-cells in reactive conditions such as *H. pylori* associated gastritis, lymphoepithelial sialadenitis and Hashimoto thyroiditis, and their subsequent clonal progression to an overt MALT lymphoma have been well described in literature [33-37].

Apart from malignant transformation, the immune and inflammatory responses are also critical for sustaining the growth and survival of the transformed cells. This is best illustrated by the findings that a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin can be successfully treated by eradication of the associated microbial organisms using antibiotics [38-41]. The potential factors that sustain malignant B-cells are numerous. The immune responses generate a network of B-cell helper signals, such as those from T-cells, dendritic cells and innate lymphoid cells, which are also potentially important for malignant B-cells. In addition, the inflammatory responses likely produce further growth factors and cytokines, which may support malignant B-cells. Despite numerous potential helper signals from the immune and inflammatory responses, the occurrence of MALT lymphoma is rather a rare event, indicating a highly selective process for B-cell clones that acquire certain immunological properties, such as aberrant responses to their microenvironment. Although not yet fully investigated, there is evidence to suggest that several surface receptor signalling may underpin the immunological drive in development of MALT lymphoma.

3. Immunological drive

3.1. BCR signalling

i) Biased IG gene usage in MALT lymphoma

Sequence analysis of the rearranged IG genes in MALT lymphoma shows evidence of positive or negative selection of replacement mutations, indicating antigen mediated affinity maturation. There is increasing evidence showing that there is a biased usage of certain IG genes in MALT lymphoma, particularly in those of the stomach, ocular adnexa and salivary gland where a relatively reasonable number of cases has been investigated. In the vast majority of the related studies, particularly those of earlier investigations, the focus is largely on the analysis of the rearranged IG heavy chain genes. In general, MALT lymphoma of the ocular adnexa and salivary glands clearly show a significantly biased usage of IGHV4-34 and IGHV1-69 respectively, while those of the stomach appear to show over-representation of IGHV3-7 and IGHV1-69 usage (Table 1). Although not yet fully characterised, the biased usage of IGHV4-34 and IGHV1-69 in MALT lymphoma are also in association with a biased usage of IG light chain genes (IGKV3-20) [42,43], further arguing for their recognition of defined antigenic determinants. Interestingly, the biased usage of IGHV4-34 in ocular adnexal MALT lymphoma is far more prevalent in those negative for *Chlamydia psittaci* [44].

ii) Properties of immunoglobulin expressed by MALT lymphoma.

Despite the causative relationship between microbial infection and MALT lymphoma at several anatomic sites, there is no evidence yet showing that the lymphoma derived immunoglobulin recognises microbial antigens [42,43,62]. Instead, there is mounting evidence indicating that at least a high proportion of immunoglobulins expressed by MALT lymphoma of various sites are auto-reactive as shown by analysis of their recombinant antibodies and/or demonstration of their high homology to a stereotypic complementarity determining region 3 (CDR3) sequence, such as those of rheumatoid factors (RF) (Table 2).

In a large survey of lymphoma derived IG gene sequences for homology to RF associated stereotypic CDR3 sequences, Bende and colleagues have demonstrated that a high proportion of MALT lymphoma of the salivary gland (41%) and stomach (18%), but not those from the lung, harbour significant homology to the CDR3 sequences of canonical RFs (IGHV1-69-RF, IGHV3-7-RF and WOL-RF) [42]. *In vitro* binding analysis of the recombinant antibodies from the representative MALT lymphoma associated IGHV1-69 or IGHV3-7 rearrangements confirms their activities to the Fc portion of human IgG [42]. Moreover, strong RF activities are also demonstrated for recombinant antibodies from two MALT lymphomas that harbour classic RF IGHV1-69/IGHJ4 rearrangement, but not yet meet the criteria for a high homology to a RF CDR3 sequence, and additionally from a HCV-associated MALT lymphoma that harbours a novel IGHV4-59/IGHJ5 stereotypic rearrangement [42,63]. These findings indicate that the true frequency of MALT lymphomas that express BCR bearing RF activities is underestimated.

The IGHV4-34 rearrangement frequently seen in ocular adnexal MALT lymphoma is also most likely autoreactive. Autoantibodies encoded by IGHV4-34 rearrangement in reactive B-cells are known for their dependence on the unique and conserved germline FR1 hydrophobic patch (Q⁶W⁷ and A²⁴V²⁵Y²⁶), which is critical for binding to *N*-acetyl-lactosamine residues, present in a wide range of surface glycoproteins [64]. Importantly, the germline FR1 hydrophobic patch is commonly spared by somatic mutations in lymphomas including ocular adnexal MALT lymphoma (personal communication with Dr Richard Bende, July 2016) [65]. Furthermore, analysis of recombinant antibodies from MALT lymphomas that harbour IGHV4-34 rearrangement confirms their polyreactivity [43].

Apart from the above well-characterised IG gene rearrangements that encode autoantibodies, there is further evidence of polyreactivity of MALT lymphoma associated-BCRs encoded by other IG gene

rearrangements such as those involving IGHV3-23 and IGHV3-30, IGHV3-33 and IGHV3-66, as shown by several recombinant antibody studies [42,43,48,62]. As the number of cases investigated to date is small, the extent of autoreactive BCR expressed by MALT lymphoma is likely not yet fully appreciated.

iii) Evidence of BCR signalling is operational in MALT lymphoma

There are several strands of evidence indicating that the BCR expressed by MALT lymphoma cells is operational. The lymphoma cells almost always express surface IgM, and possess a range of biological properties of reactive B-cells including ability to undergo blast transformation, plasma cell differentiation and even further “germinal centre reaction”, known as follicular colonisation [66,67]. While in the colonised follicles, MALT lymphoma cells show active proliferation and similar phenotypic changes like reactive B-cells. Genetically, MALT lymphoma cells frequently exhibit intraclonal variations or ongoing mutations in their rearranged IG genes, which are probably the result of their follicular colonisation of reactive B-cell follicles [45,53,68-70]. Like normal B-cells, these phenotypic and genetic changes in MALT lymphoma cells are most likely the result of their responses to microenvironment milieu including stimulation through surface BCR, co-stimulating receptors and cytokine receptors. **It is highly likely that BCR engagement by autoantigen triggers a chronic and active BCR signalling, thus causes NF- κ B activation, consequently enhancing the lymphoma cell survival and proliferation.** In line with this, crosslinking surface IgM on MALT lymphoma cells is capable of stimulating their proliferation or enhancing their proliferative responses to mitogens [71]. **Nonetheless, BCR engagement alone is unlikely sufficient to maintain the growth and survival of MALT lymphoma cells in view of the evidence that a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin show complete regression following anti-microbial treatment. Thus, the immune and inflammatory responses other than direct BCR stimulation, which are eliminated following anti-microbial treatment, may be the major player in sustaining the survival of lymphoma cells.**

3.2. T-cell help and CD40 signalling

Among the many B-cell helper signals present in the microenvironment of MALT lymphoma, only T-cell help has been fairly investigated and this is largely based on studies of gastric MALT lymphoma. Although gastric MALT lymphoma is causatively linked to chronic *H. pylori* infection, *H. pylori* antigens do not directly stimulate the neoplastic B-cells, but rather activate *H. pylori* specific tumour infiltrating T-cells and through them to promote the survival and proliferation of lymphoma B-cells [62,72]. This involves cognate interaction between B and T-cells [73-75], and also bystander T-cell help via soluble ligands and cytokines, such as CD40L and BAFF, thus activating the non-canonical NF- κ B pathway (Figure 1) [76]. In support of this, reactive B-cell follicles are invariably present in gastric MALT lymphoma, and these reactive components provide a setting for classical immunological responses that generate *H. pylori* specific T-cells. An enriched expression of proinflammatory cytokines such as IL8 and IL1 β , molecules involved in B and T-cell interaction such as CD86, CD28 and ICOS is seen in gastric MALT lymphoma, particularly those without chromosome translocation [77]. In addition, in the mouse model of *Helicobacter* induced gastric MALT lymphoma, Th2 cytokines such as IL4, rather than CD40 signalling, have been thought to play a critical role in the proliferation of lymphoma cells [78].

Clearly, the immune and inflammatory responses are critical for the evolution and emergence of autoreactive cells, their malignant transformation and subsequent clonal expansion. Although the survival of MALT lymphoma cells in a high proportion of cases is still highly dependent on such immunological drive, such an effect of immunological drive is likely additive or synergistic to those conferred by acquired genetic changes as immunological drive alone is not sufficient for malignant transformation.

4. Genetic abnormalities

The spectrum of genetic abnormalities underlying the molecular mechanisms of MALT lymphoma has not been explored by whole genome or whole exome sequencing, and thus remains to be fully investigated.

Despite this, various genetic abnormalities identified in MALT lymphoma to date have been shown commonly targeting the signalling pathways that regulate the NF- κ B activities. These genetic abnormalities include chromosome translocations, somatic mutations and copy number changes, and intriguingly occur at remarkably variable frequencies in MALT lymphoma of different anatomic sites despite targeting the same or a similar molecular pathway.

4.1. **t(1;14)(p22;q32)/BCL10-IGH**

This translocation occurs primarily in MALT lymphoma of the lung (9%) and stomach (4%) (Figure 3), and juxtaposes the *BCL10* gene under the regulatory control of the IG gene enhancer, leading to BCL10 over-expression (Figure 4) [79-81]. BCL10 is an essential component of the CARD11/BCL10/MALT1 signalosome complex that relays the antigen receptor signalling to the canonical NF- κ B activation pathway (Figures 1 & 5) [6,82]. Over-expression of BCL10 causes its constitutive activation through oligomerisation via its N-terminal CARD/CARD interaction, and thus leads to enhanced NF- κ B activities. Intriguingly, BCL10 protein is aberrantly expressed in the nuclei of lymphoma cells with t(1;14)(p22;q32)/*BCL10-IGH* or t(11;18)(q21;q21)/*BIRC3 (API2)-MALT1*, and also in the marginal zone B-cells of Eu-BCL10 mice [79,83-86], suggesting a yet unappreciated role of nuclear BCL10 in the pathogenesis of MALT lymphoma.

Apart from the canonical NF- κ B pathway as detailed above, there is also evidence for a role of BCL10 in the regulation of non-canonical NF- κ B pathway. Bcl10 deficiency B-cells show a reduced expression of NF- κ B2 (p100), and also a reduced nuclear accumulation of the non-canonical p52/RelB complex following BAFF stimulation [87]. In contrast, B-cells in E μ -BCL10 mice exhibited constitutive activation of both canonical and non-canonical NF- κ B signalling pathways, and the activation of non-canonical pathway was thought to be indirect via up-regulation of BAFF expression [86]. In keeping with these findings, BAFF has been shown to be over-expressed in MALT lymphoma [88,89].

4.2. **t(14;18)(q32;q21)/IGH-MALT1**

This translocation occurs mainly in MALT lymphoma of the ocular adnexa (7%) and lung (6%) (Figure 3), and causes MALT1 over-expression [90-92]. MALT1 contains several functional domains including an N-terminal death domain, three immunoglobulin-like domains and a proteolytically active caspase-like domain (Figure 4). Through its two N-terminal Ig-like domains, MALT1 interacts with BCL10, triggering its own oligomerisation and activation, thus enhances canonical NF- κ B signalling (Figures 1 & 5) [93,94]. This is supported by a strong accumulation of both MALT1 and BCL10 in the cytoplasm of the lymphoma cells carrying t(14;18)(q32;q21)/*IGH-MALT1*, a very distinct expression pattern from those of MALT lymphoma with t(1;14)(p22;q32)/*BCL10-IGH* or t(11;18)(q21;q21)/*BIRC3 (API2)-MALT1* [90].

Through its protease activities, MALT1 also regulates NF- κ B activation by specific cleavage of several NF- κ B regulators including TNFAIP3 (A20), CYLD, RelB and BCL10, thus inactivating the function of these proteins [95-98]. Among these, TNFAIP3, CYLD and RelB are NF- κ B negative regulators and are thus particularly relevant in lymphoma pathogenesis [95-99]. For example, TNFAIP3 is a transcriptional target of NF- κ B, serves as a “global” feedback regulator to attenuate NF- κ B activity by inactivation of NEMO, TRAF6, and RIP1, thus negatively regulating several cellular signalling that activate the canonical NF- κ B pathway (Figures 1 & 5) [12,100-102]. Constitutive activation of MALT1 by translocation may abolish the above NF- κ B negative regulators, eliminating the physiological auto-negative feedback and causing relentless NF- κ B activation.

MALT1 also plays a role in regulation of non-canonical NF- κ B activation pathway, and its deficiency in B-cells significantly reduces the BAFF-induced phosphorylation and degradation of NF- κ B2 (p100), thus decreases transcriptionally active p52 [103]. Consequently, MALT1 deficiency significantly impairs BAFF-induced cell survival, and interestingly this affects only marginal zone B-cell, but not follicular B-cells [103]. These

findings suggest that over-expression MALT1 by chromosome translocation may also lead to dysregulation of the non-canonical NF-κB activation pathway.

In addition, MALT1 can directly interact with and activate caspase-8 in a protease independent manner, and direct its function to activate the NF-κB pathway rather than apoptosis pathway upon antigen receptor stimulation in T-cells [104,105]. It remains to be investigated whether this MALT1 function is also operational in B-cells, hence has a potential role in lymphoma pathogenesis.

4.3. t(11;18)(q21;q21)/BIRC3(API2)-MALT1

This translocation occurs predominantly in MALT lymphoma of the stomach (24%), lung (38%) (Figure 3) [90,91], and causes a chimeric fusion between the N-terminal API2 and the C-terminal MALT1 (Figure 4) [106-108]. The resulting API2-MALT1 fusion product gains novel abilities to confer oncogenic activities via activation of both canonical and non-canonical NF-κB pathways (Figure 5).

The API2-MALT1 fusion products are also capable of auto-oligomerisation through heterotypic interaction between the BIR1 of the API2 moiety and the C-terminal region of MALT1, thus resulting in constitutive activation of the canonical NF-κB pathway [109,110]. Like MALT1, API2-MALT1 can also cleave TNFAIP3/A20 and CYLD and eliminate these physiological negative feedback regulations (Figure 5) [95,111]. In addition, the API2-MALT1 induced NF-κB activation may enhance its own expression since API2 is a transcriptional target of NF-κB [112]. In keeping with this speculation, high levels of polyubiquitination of NEMO are seen in MALT lymphomas with t(11;18)(q21;q21)/API2-MALT1 and also in marginal zone B-cells of Eμ-API2-MALT1 mice [110,113].

The API2-MALT1 fusion product also gains ability to activate the non-canonical NF-κB pathway (Figure 5). The API2 moiety of the fusion product recruits NIK and places it in close proximity with the activated MALT1 protease domain, leading to cleavage of NIK at arginine 325. This generates a C-terminal NIK fragment that retains kinase activity and resists to TRAF3 dependent proteasomal degradation, and consequently causes constitutive signalling to activate the non-canonical NF-κB pathway [114].

Furthermore, the API2-MALT1 fusion product cleaves the tumour suppresser protein LIMA1 (LIM domain and actin-binding protein-1) via concerted actions of the API2 moiety and MALT1 caspase-like domain, and generates a novel oncogenic LIM domain-only (LMO) fragment (Figure 5) [115]. Expression of the LMO fragment promotes survival and proliferation of primary B-cells *in vitro* and tumour formation in xenograft model [115], albeit its molecular mechanism remains to be investigated.

4.4. TNFAIP3 (A20) inactivation

TNFAIP3 deletion and/or inactivation mutation are largely seen in MALT lymphomas of the ocular adnexa, salivary gland and thyroid, in which the above chromosome translocations are absent or rare (Figure 3) [116-120]. Unlike the above chromosome translocations that are specific to MALT lymphoma, TNFAIP3/A20 deletion and inactivating mutations are also frequently seen in a range of other lymphoma entities [119-124]. TNFAIP3 contains an N-terminal OTU domain that possesses deubiquitinating activity, and 7 zinc finger domains in its C-terminus, which confers the E3 ubiquitin ligase activity (Figure 4) [10,100]. Through removing the K63-linked ubiquitin chain, catalysing the K48-linked polyubiquitination and also direct binding to the linear polyubiquitin chain of its targets, TNFAIP3 can inactivate several NF-κB positive regulators including RIP1/2, TRAF6 and IKKγ (Figure 1) [12,101,102]. Thus, TNFAIP3 inactivation can potentially augment NF-κB activation triggered by signalling from multiple surface receptors.

4.5. MYD88 mutation:

This occurs in ~5% of ocular adnexal MALT lymphoma, and comprises novel inframe deletions as well as previously identified hotspot mutations such as L265P in the TIR domain, which is found frequently in several other B-cell lymphoma subtypes (Figures 3 & 4) [125-129]. These different mutations have been shown to be a gain-of-function change [125,127]. MYD88 mutants are constitutively active and capable of spontaneously assembling a protein complex containing IRAK1 and IRAK4, thus signalling to activate NF- κ B, STAT3 and AP1 transcription factors (Figure 1) [125].

Somatic mutations in other NF- κ B regulators: Although this has not yet been comprehensively investigated, several studies show that the somatic mutations of other NF- κ B regulators including CD79A, CD79B, CARD11, BIRC3, TRAF3 and TNFRSF11A, which are frequently seen in several B-cell lymphomas characterised by constitutive NF- κ B activation, are rare in MALT lymphoma [126-128,130-132]. The extent of common and unique genetic abnormalities between MALT lymphoma and other B-cell lymphomas characterised with constitutive NF- κ B activities remains to be investigated.

4.6. Other chromosome translocations:

There are also several novel chromosome translocations including t(3;14)(p13;q32)/*FOXP1-IGH* [133-135], t(1;14)(p21;q32)/*CNN3-IGH*, t(5;14)(q34;q32)/*ODZ2-IGH*, t(9;14)(p24;q32)/*JMJD2C-IGH* [136] and t(X;14)(p11.4;q32)/*GPR34-IGH* [137,138], which are reported in isolated cases of MALT lymphoma. These translocations are predicted to cause over-expression of the oncogene involved as these are in association with the IGH gene locus, thus under the transcriptional control of the IG gene enhancer. The molecular mechanism underlying the oncogenic activities of these genetic events remains to be investigated.

5. Oncogenic cooperation among immunological stimulation and genetic changes

There is firm evidence that none of the genetic abnormalities in MALT lymphoma alone is sufficient for malignant transformation. Both E μ -*BCL10* and E μ -*API2-MALT1* mice develop splenic marginal zone hyperplasia but not lymphoma [86,113], while *TNFAIP3* (A20) deficiency in B-cells enhances B-cell proliferation with an excessive production of self-reactive autoantibodies [139]. However, stimulation of E μ -*API2-MALT1* mice with Freund's complete adjuvant leads to development of splenic marginal zone lymphoma-like lesion [140], suggesting oncogenic cooperation between genetic abnormalities and immunological stimulations.

As discussed above, there is a considerable overlap in the signalling pathways dysregulated by immunological stimulations and genetic changes (Figure 5). For example, the receptor signalling that leads to canonical NF- κ B pathway activation, such as BCR and TLR (toll-like receptor), and those resulting in non-canonical NF- κ B pathway activation such as BAFFR and CD40, are affected by both immunological stimulations and genetic changes. These signalling pathways and their concerted actions are known to be critical for the development and function of marginal zone B-cells [141,142]. Such biological cooperation among different receptor signalling is likely operational in MALT lymphoma cells, but in a remarkably dysregulated manner due to constitutive activations by auto-reactive BCR and genetic changes. For example, the constitutive activation of both canonical and non-canonical NF- κ B pathways by chromosome translocation can be further augmented by chronic stimulation of surface BCR, TLR, BAFFR and CD40 [77]. Similarly, the BCR and TLR receptor signalling conferred by microenvironment milieu can be enhanced by *TNFAIP3* (A20) inactivation via genetic changes. Clearly, the extent of potential oncogenic cooperation among immunological responses and genetic abnormalities is very much underestimated due to incomplete understanding of the signalling for marginal zone B-cell development as well as incomplete characterisation of the genetics of MALT lymphoma.

6. Summary and future prospective

MALT lymphoma is a paradigm for illustration of oncogenic cooperation between immunological drive and genetic abnormalities in lymphoma genesis. There are significant differences in the aetiology, IG gene usage and acquired genetic changes in MALT lymphoma of different anatomic sites despite they all share certain common clinicopathological features, and such variations offer excellent opportunities for discovery research. Particularly, neither the immunological drive nor genetic changes have been comprehensively investigated in MALT lymphoma of different anatomic sites. It is imperative to perform whole genome or exome sequencing analysis to characterise the somatic mutation profile of MALT lymphoma of various anatomic sites and dissect their molecular oncogenic mechanisms. It is also important to comprehensively catalogue IG gene usage in MALT lymphoma of various anatomic sites, and characterise the properties of the lymphoma derived immunoglobulin. Finally, apart from T helper cells, it is important to investigate the potential role of other B-cell helper signals, such as those from dendritic cells, neutrophils and innate lymphoid cells, in the pathogenesis of MALT lymphoma, in light of their important role in the biology of normal B-cells [143,144]. A comprehensive investigation of these genetic and immunological properties will provide rich information and insights into the molecular mechanisms and oncogenic cooperation among somatic genetic abnormalities and immunological stimulations in MALT lymphoma.

Acknowledgements:

The studies described from the Professor Ming-Qing Du's laboratory were supported by research grants from Bloodwise, U.K., Kay Kendall Leukaemia Fund, the Elimination of Leukemia Fund, U.K., the Lady Tata Memorial Trust, U.K, and the Addenbrooke's Charitable Trust.

References:

1. Rickert RC. New insights into pre-BCR and BCR signalling with relevance to B cell malignancies. *Nat Rev Immunol* 2013;13: 578-91.
2. Seda V, Mraz M. B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. *Eur J Haematol* 2015;94: 193-205.
3. Rawlings DJ, Schwartz MA, Jackson SW, Meyer-Bahlburg A. Integration of B cell responses through Toll-like receptors and antigen receptors. *Nat Rev Immunol* 2012;12: 282-94.
4. De Nardo D. Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine* 2015;74: 181-9.
5. Rawlings DJ, Sommer K, Moreno-Garcia ME. The CARMA1 signalosome links the signalling machinery of adaptive and innate immunity in lymphocytes. *Nat Rev Immunol* 2006;6: 799-812.
6. Thome M, Weil R. Post-translational modifications regulate distinct functions of CARMA1 and BCL10. *Trends Immunol* 2007;28: 281-8.
7. Yang C, David L, Qiao Q, Damko E, Wu H. The CBM signalosome: potential therapeutic target for aggressive lymphoma? *Cytokine Growth Factor Rev* 2014;25: 175-83.
8. Sun L, Deng L, Ea CK, Xia ZP, Chen ZJ. The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol Cell* 2004;14: 289-301.
9. Sasaki Y, Iwai K. Roles of the NF-kappaB Pathway in B-Lymphocyte Biology. *Curr Top Microbiol Immunol* 2016;393: 177-209.
10. Sun SC. Deubiquitylation and regulation of the immune response. *Nat Rev Immunol* 2008;8: 501-11.
11. Sun SC, Ley SC. New insights into NF-kappaB regulation and function. *Trends Immunol* 2008;29: 469-78.
12. Vereecke L, Beyaert R, Van Loo G. The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology. *Trends Immunol* 2009;30: 383-91.
13. Skaug B, Chen J, Du F, He J, Ma A, Chen ZJ. Direct, noncatalytic mechanism of IKK inhibition by A20. *Mol Cell* 2011;44: 559-71.
14. Catrysse L, Vereecke L, Beyaert R, Van Loo G. A20 in inflammation and autoimmunity. *Trends Immunol* 2014;35: 22-31.
15. Yang XD, Sun SC. Targeting signaling factors for degradation, an emerging mechanism for TRAF functions. *Immunol Rev* 2015;266: 56-71.
16. Staudt LM. Oncogenic activation of NF-kappaB. *Cold Spring Harb Perspect Biol* 2010;2: a000109.
17. Shaffer AL, III, Young RM, Staudt LM. Pathogenesis of human B cell lymphomas. *Annu Rev Immunol* 2012;30: 565-610.
18. Isaacson PG, Chott A, Nakamura S, Muller-Hermelink HK, Harris NL and Swerdlow SH. Extranodal marginal lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J and Vardiman JW, editors. WHO classification of

tumours of haematopoietic and lymphoid tissues,. Lyon: International Agency for Research on Cancer; 2008, p. 214-7

19. Garbe C, Stein H, Dienemann D, Orfanos CE. *Borrelia burgdorferi*-associated cutaneous B cell lymphoma: clinical and immunohistologic characterization of four cases. *J Am Acad Dermatol* 1991;24: 584-90.
20. Cerroni L, Zochling N, Putz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997;24: 457-61.
21. Sonck CE, Viljanen M, Hirsimaki P, Soderstrom KO, Ekfors TO. Borrelial lymphocytoma--a historical case. *APMIS* 1998;106: 947-52.
22. Goodlad JR, Davidson MM, Hollowood K, Ling C, MacKenzie C, Christie I, et al. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the Highlands of Scotland. *Am J Surg Pathol* 2000;24: 1279-85.
23. Grange F, Wechsler J, Guillaume JC, Tortel J, Tortel MC, Audhuy B, et al. *Borrelia burgdorferi*-associated lymphocytoma cutis simulating a primary cutaneous large B-cell lymphoma. *J Am Acad Dermatol* 2002;47: 530-4.
24. Bogle MA, Riddle CC, Triana EM, Jones D, Duvic M. Primary cutaneous B-cell lymphoma. *J Am Acad Dermatol* 2005;53: 479-84.
25. Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell'Oro S, Fleischhauer K, et al. Evidence for an association between *Chlamydia psittaci* and ocular adnexal lymphomas. *J Natl Cancer Inst* 2004;96: 586-94.
26. Rosado MF, Byrne GE, Jr., Ding F, Fields KA, Ruiz P, Dubovy SR, et al. Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with *Chlamydia psittaci*. *Blood* 2006;107: 467-72.
27. Vargas RL, Fallone E, Felgar RE, Friedberg JW, Arbin AA, Andersen AA, et al. Is there an association between ocular adnexal lymphoma and infection with *Chlamydia psittaci*? The University of Rochester experience. *Leuk Res* 2006;30: 547-51.
28. Chanudet E, Zhou Y, Bacon CM, Wotherspoon AC, Muller-Hermelink HK, Adam P, et al. *Chlamydia psittaci* is variably associated with ocular adnexal MALT lymphoma in different geographical regions. *J Pathol* 2006;209: 344-51.
29. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. *N Engl J Med* 2004;350: 239-48.
30. Voulgarelis M, Moutsopoulos HM. Mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: risks, management, and prognosis. *Rheum Dis Clin North Am* 2008;34: 921-33, viii.
31. Watanabe N, Noh JY, Narimatsu H, Takeuchi K, Yamaguchi T, Kameyama K, et al. Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24553 patients with Hashimoto's disease. *Br J Haematol* 2011;153: 236-43.
32. Ferreri AJ, Govi S, Ponzoni M. Marginal zone lymphomas and infectious agents. *Semin Cancer Biol* 2013;23: 431-40.

33. Nakamura S, Aoyagi K, Furuse M, Suekane H, Matsumoto T, Yao T, et al. B-cell monoclonality precedes the development of gastric MALT lymphoma in Helicobacter pylori-associated chronic gastritis. *Am J Pathol* 1998;152: 1271-9.
34. Diss TC, Wotherspoon AC, Speight PM, Pan LX, Isaacson PG. B cell monoclonality, Epstein Barr virus and t(14;18) in myoepithelial sialadenitis and low grade B cell MALT lymphoma of the parotid gland. *Am J Surg Pathol* 1995;19: 531-6.
35. Zucca E, Bertoni F, Roggero E, Bosshard G, Cazzaniga G, Pedrinis E, et al. Molecular analysis of the progression from Helicobacter pylori-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach. *N Engl J Med* 1998;338: 804-10.
36. Bahler DW, Swerdlow SH. Clonal salivary gland infiltrates associated with myoepithelial sialadenitis (Sjogren's syndrome) begin as nonmalignant antigen-selected expansions. *Blood* 1998;91: 1864-72.
37. Moshynska OV, Saxena A. Clonal relationship between Hashimoto thyroiditis and thyroid lymphoma. *J Clin Pathol* 2008;61: 438-44.
38. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet* 1993;342: 575-7.
39. Ruskone-Fourmesttraux A, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut* 2011;60: 747-58.
40. Ferreri AJ, Ponzoni M, Guidoboni M, De Conciliis C, Resti AG, Mazzi B, et al. Regression of ocular adnexal lymphoma after Chlamydia psittaci-eradicating antibiotic therapy. *J Clin Oncol* 2005;23: 5067-73.
41. Roggero E, Zucca E, Mainetti C, Bertoni F, Valsangiacomo C, Pedrinis E, et al. Eradication of Borrelia burgdorferi infection in primary marginal zone B-cell lymphoma of the skin. *Hum Pathol* 2000;31: 263-8.
42. Bende RJ, Aarts WM, Riedl RG, de Jong D, Pals ST, van Noesel CJ. Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity. *J Exp Med* 2005;201: 1229-41.
43. Zhu D, Bhatt S, Lu X, Guo F, Veelken H, Hsu DK, et al. Chlamydia psittaci-negative ocular adnexal marginal zone lymphomas express self polyreactive B-cell receptors. *Leukemia* 2015;29: 1587-99.
44. van Maldegem F, Wormhoudt TA, Mulder MM, Oud ME, Schilder-Tol E, Musler AR, et al. Chlamydia psittaci-negative ocular adnexal marginal zone B-cell lymphomas have biased VH4-34 immunoglobulin gene expression and proliferate in a distinct inflammatory environment. *Leukemia* 2012;26: 1647-53.
45. Thiede C, Alpen B, Morgner A, Schmidt M, Ritter M, Ehninger G, et al. Ongoing somatic mutations and clonal expansions after cure of Helicobacter pylori infection in gastric mucosa-associated lymphoid tissue B-cell lymphoma. *J Clin Oncol* 1998;16: 3822-31.
46. Michaeli M, Tabibian-Keissar H, Schiby G, Shahaf G, Pickman Y, Hazanov L, et al. Immunoglobulin gene repertoire diversification and selection in the stomach - from gastritis to gastric lymphomas. *Front Immunol* 2014;5: 264.
47. Sakuma H, Nakamura T, Uemura N, Chiba T, Sugiyama T, Asaka M, et al. Immunoglobulin VH gene analysis in gastric MALT lymphomas. *Mod Pathol* 2007;20: 460-6.

48. Craig VJ, Arnold I, Gerke C, Huynh MQ, Wundisch T, Neubauer A, et al. Gastric MALT lymphoma B cells express polyreactive, somatically mutated immunoglobulins. *Blood* 2010;*115*: 581-91.
49. De R, V, De Vita S, Marzotto A, Rupolo M, Gloghini A, Pivetta B, et al. Sequence analysis of the immunoglobulin antigen receptor of hepatitis C virus-associated non-Hodgkin lymphomas suggests that the malignant cells are derived from the rheumatoid factor-producing cells that occur mainly in type II cryoglobulinemia. *Blood* 2000;*96*: 3578-84.
50. Coupland SE, Foss HD, Anagnostopoulos I, Hummel M, Stein H. Immunoglobulin VH gene expression among extranodal marginal zone B-cell lymphomas of the ocular adnexa. *Invest Ophthalmol Vis Sci* 1999;*40*: 555-62.
51. Mannami T, Yoshino T, Oshima K, Takase S, Kondo E, Ohara N, et al. Clinical, histopathological, and immunogenetic analysis of ocular adnexal lymphoproliferative disorders: characterization of malt lymphoma and reactive lymphoid hyperplasia. *Mod Pathol* 2001;*14*: 641-9.
52. Bahler DW, Szankasi P, Kulkarni S, Tubbs RR, Cook JR, Swerdlow SH. Use of similar immunoglobulin VH gene segments by MALT lymphomas of the ocular adnexa. *Mod Pathol* 2009;*22*: 833-8.
53. Zhu D, Lossos C, Chapman-Fredricks JR, Matthews JM, Ikpatt OF, Ruiz P, et al. Biased use of the IGHV4 family and evidence for antigen selection in *Chlamydia psittaci*-negative ocular adnexal extranodal marginal zone lymphomas. *PLoS One* 2011;*6*: e29114.
54. Dagklis A, Ponzoni M, Govi S, Cangini MG, Pasini E, Charlotte F, et al. Immunoglobulin gene repertoire in ocular adnexal lymphomas: hints on the nature of the antigenic stimulation. *Leukemia* 2012;*26*: 814-21.
55. Bahler DW, Miklos JA, Swerdlow SH. Ongoing Ig gene hypermutation in salivary gland mucosa-associated lymphoid tissue-type lymphomas. *Blood* 1997;*89*: 3335-44.
56. Miklos JA, Swerdlow SH, Bahler DW. Salivary gland mucosa-associated lymphoid tissue lymphoma immunoglobulin V(H) genes show frequent use of V1-69 with distinctive CDR3 features. *Blood* 2000;*95*: 3878-84.
57. Sato Y, Nakamura N, Nakamura S, Sakugawa S, Ichimura K, Tanaka T, et al. Deviated VH4 immunoglobulin gene usage is found among thyroid mucosa-associated lymphoid tissue lymphomas, similar to the usage at other sites, but is not found in thyroid diffuse large B-cell lymphomas. *Mod Pathol* 2006;*19*: 1578-84.
58. Tierens A, Delabie J, Pittaluga S, Driessen A, DeWolf-Peters C. Mutation analysis of the rearranged immunoglobulin heavy chain genes of marginal zone cell lymphomas indicates an origin from different marginal zone B lymphocyte subsets. *Blood* 1998;*91*: 2381-6.
59. Bahler DW, Kim BK, Gao A, Swerdlow SH. Analysis of immunoglobulin V genes suggests cutaneous marginal zone B-cell lymphomas recognise similar antigens. *Br J Haematol* 2006;*132*: 571-5.
60. Perez M, Pacchiarotti A, Frontani M, Pescarmona E, Caprini E, Lombardo GA, et al. Primary cutaneous B-cell lymphoma is associated with somatically hypermutated immunoglobulin variable genes and frequent use of VH1-69 and VH4-59 segments. *Br J Dermatol* 2010;*162*: 611-8.
61. Kurosu K, Yumoto N, Furukawa M, Kuriyama T, Mikata A. Low-grade pulmonary mucosa-associated lymphoid tissue lymphoma with or without intraclonal variation. *Am J Respir Crit Care Med* 1998;*158*: 1613-9.

62. Hussell T, Isaacson PG, Crabtree JE, Dogan A, Spencer J. Immunoglobulin specificity of low grade B cell gastrointestinal lymphoma of mucosa-associated lymphoid tissue (MALT) type. *Am J Pathol* 1993;**142**: 285-92.
63. Bende RJ, Janssen J, Wormhoudt TA, Wagner K, Guikema JE, van Noesel CJ. Identification of a novel stereotypic IGHV4-59/IGHJ5-encoded B-cell receptor subset expressed by various B-cell lymphomas with high affinity rheumatoid factor activity. *Haematologica* 2016;
64. Richardson C, Chida AS, Adlowitz D, Silver L, Fox E, Jenks SA, et al. Molecular basis of 9G4 B cell autoreactivity in human systemic lupus erythematosus. *J Immunol* 2013;**191**: 4926-39.
65. Young RM, Wu T, Schmitz R, Dawood M, Xiao W, Phelan JD, et al. Survival of human lymphoma cells requires B-cell receptor engagement by self-antigens. *Proc Natl Acad Sci U S A* 2015;**112**: 13447-54.
66. Isaacson PG, Wotherspoon AC, Diss T, Pan LX. Follicular colonization in B-cell lymphoma of mucosa-associated lymphoid tissue. *Am J Surg Pathol* 1991;**15**: 819-28.
67. Isaacson PG, Androulakis Papachristou A, Diss TC, Pan L, Wright DH. Follicular colonization in thyroid lymphoma. *Am J Pathol* 1992;**141**: 43-52.
68. Du MQ, Xu CF, Diss TC, Peng HZ, Wotherspoon AC, Isaacson PG, et al. Intestinal dissemination of gastric mucosa-associated lymphoid tissue lymphoma. *Blood* 1996;**88**: 4445-51.
69. Du M, Diss TC, Xu C, Peng H, Isaacson PG, Pan L. Ongoing mutation in MALT lymphoma immunoglobulin gene suggests that antigen stimulation plays a role in the clonal expansion. *Leukemia* 1996;**10**: 1190-7.
70. Qin Y, Greiner A, Hallas C, Haedicke W, Muller Hermelink HK. Intracлонаl offspring expansion of gastric low-grade MALT-type lymphoma: evidence for the role of antigen-driven high-affinity mutation in lymphomagenesis. *Lab Invest* 1997;**76**: 477-85.
71. Hussell T, Isaacson PG, Spencer J. Proliferation and differentiation of tumour cells from B-cell lymphoma of mucosa-associated lymphoid tissue in vitro. *J Pathol* 1993;**169**: 221-7.
72. D'Elis MM, Amedei A, Manghetti M, Costa F, Baldari CT, Quazi AS, et al. Impaired T-cell regulation of B-cell growth in *Helicobacter pylori*-related gastric low-grade MALT lymphoma. *GASTROENTEROLOGY* 1999;**117**: 1105-12.
73. Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet* 1993;**342**: 571-4.
74. Hussell T, Isaacson PG, Crabtree JE, Spencer J. *Helicobacter pylori*-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low- grade gastric lymphoma of mucosa-associated lymphoid tissue. *J Pathol* 1996;**178**: 122-7.
75. Greiner A, Knorr C, Qin Y, Sebald W, Schimpl A, Banchereau J, et al. Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT-type) require CD40-mediated signaling and Th2-type cytokines for in vitro growth and differentiation. *Am J Pathol* 1997;**150**: 1583-93.
76. Bernasconi NL, Traggiai E, Lanzavecchia A. Maintenance of serological memory by polyclonal activation of human memory B cells. *Science* 2002;**298**: 2199-202.

77. Hamoudi RA, Appert A, Ye H, Ruskone-Fourmesttraux A, Streubel B, Chott A, et al. Differential expression of NF-kappaB target genes in MALT lymphoma with and without chromosome translocation: insights into molecular mechanism. *Leukemia* 2010;24: 1487-97.
78. Craig VJ, Cogliatti SB, Arnold I, Gerke C, Balandat JE, Wundisch T, et al. B-cell receptor signaling and CD40 ligand-independent T cell help cooperate in Helicobacter-induced MALT lymphomagenesis. *Leukemia* 2010;24: 1186-96.
79. Ye H, Liu H, Attygalle A, Wotherspoon AC, Nicholson AG, Charlotte F, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of H pylori in gastric MALT lymphoma. *Blood* 2003;102: 1012-8.
80. Willis TG, Jadayel DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999;96: 35-45.
81. Zhang Q, Siebert R, Yan M, Hinzmann B, Cui X, Xue L, et al. Inactivating mutations and overexpression of BCL10, a caspase recruitment domain-containing gene, in MALT lymphoma with t(1;14)(p22;q32). *Nat Genet* 1999;22: 63-8.
82. Turvey SE, Durandy A, Fischer A, Fung SY, Geha RS, Gewies A, et al. The CARD11-BCL10-MALT1 (CBM) signalosome complex: Stepping into the limelight of human primary immunodeficiency. *J Allergy Clin Immunol* 2014;134: 276-84.
83. Ye H, Dogan A, Karran L, Willis TG, Chen L, Wlodarska I, et al. BCL10 expression in normal and neoplastic lymphoid tissue : nuclear localization in MALT lymphoma. *Am J Pathol* 2000;157: 1147-54.
84. Liu H, Ye H, Dogan A, Ranaldi R, Hamoudi RA, Bearzi I, et al. T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. *Blood* 2001;98: 1182-7.
85. Maes B, Demunter A, Peeters B, Wolf-Peeters C. BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. *Blood* 2002;99: 1398-404.
86. Li Z, Wang H, Xue L, Shin DM, Roopenian D, Xu W, et al. Emu-BCL10 mice exhibit constitutive activation of both canonical and noncanonical NF-kappaB pathways generating marginal zone (MZ) B-cell expansion as a precursor to splenic MZ lymphoma. *Blood* 2009;114: 4158-68.
87. Yu M, Chen Y, He Y, Podd A, Fu G, Wright JA, et al. Critical role of B cell lymphoma 10 in BAFF-regulated NF-kappaB activation and survival of anergic B cells. *J Immunol* 2012;189: 5185-93.
88. Kuo SH, Yeh PY, Chen LT, Wu MS, Lin CW, Yeh KH, et al. Overexpression of B cell-activating factor of TNF family (BAFF) is associated with Helicobacter pylori-independent growth of gastric diffuse large B-cell lymphoma with histologic evidence of MALT lymphoma. *Blood* 2008;112: 2927-34.
89. Quartuccio L, Fabris M, Moretti M, Barone F, Bombardieri M, Rupolo M, et al. Resistance to rituximab therapy and local BAFF overexpression in Sjogren's syndrome-related myoepithelial sialadenitis and low-grade parotid B-cell lymphoma. *Open Rheumatol J* 2008;2: 38-43.
90. Ye H, Gong L, Liu H, Hamoudi RA, Shirali S, Ho L, et al. MALT lymphoma with t(14;18)(q32;q21)/IGH-MALT1 is characterized by strong cytoplasmic MALT1 and BCL10 expression. *J Pathol* 2005;205: 293-301.

91. Streubel B, Simonitsch-Klupp I, Mullauer L, Lamprecht A, Huber D, Siebert R, et al. Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. *Leukemia* 2004;18: 1722-6.
92. Streubel B, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003;101: 2335-9.
93. Uren GA, O'Rourke K, Aravind L, Pisabarro TM, Seshagiri S, Koonin VE, et al. Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. *Mol Cell* 2000;6: 961-7.
94. Lucas PC, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, et al. Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J Biol Chem* 2001;276: 19012-9.
95. Coornaert B, Baens M, Heyninck K, Bekaert T, Haegman M, Staal J, et al. T cell antigen receptor stimulation induces MALT1 paracaspase-mediated cleavage of the NF-kappaB inhibitor A20. *Nat Immunol* 2008;9: 263-71.
96. Duwel M, Welteke V, Oeckinghaus A, Baens M, Kloo B, Ferch U, et al. A20 negatively regulates T cell receptor signaling to NF-kappaB by cleaving Malt1 ubiquitin chains. *J Immunol* 2009;182: 7718-28.
97. Kirchhofer D, Vucic D. Protease activity of MALT1: a mystery unravelled. *Biochem J* 2012;444: e3-e5.
98. Bartuzi P, Hofker MH, van de SB. Tuning NF-kappaB activity: a touch of COMMD proteins. *Biochim Biophys Acta* 2013;1832: 2315-21.
99. Hailfinger S, Nogai H, Pelzer C, Jaworski M, Cabalzar K, Charton JE, et al. Malt1-dependent RelB cleavage promotes canonical NF-kappaB activation in lymphocytes and lymphoma cell lines. *Proc Natl Acad Sci U S A* 2011;108: 14596-601.
100. Coornaert B, Carpentier I, Beyaert R. A20: central gatekeeper in inflammation and immunity. *J Biol Chem* 2009;284: 8217-21.
101. Boone DL, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, et al. The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. *Nat Immunol* 2004;5: 1052-60.
102. Thome M, Tschopp J. TCR-induced NF-kappaB activation: a crucial role for Carma1, Bcl10 and MALT1. *Trends Immunol* 2003;24: 419-24.
103. Tusche MW, Ward LA, Vu F, McCarthy D, Quintela-Fandino M, Ruland J, et al. Differential requirement of MALT1 for BAFF-induced outcomes in B cell subsets. *J Exp Med* 2009;206: 2671-83.
104. Kawadler H, Gantz MA, Riley JL, Yang X. The paracaspase MALT1 controls caspase-8 activation during lymphocyte proliferation. *Mol Cell* 2008;31: 415-21.
105. Kingeter LM, Schaefer BC. Malt1 and cIAP2-Malt1 as effectors of NF-kappaB activation: kissing cousins or distant relatives? *Cell Signal* 2010;22: 9-22.
106. Dierlamm J, Baens M, Wlodarska I, Stefanova-Ouzounova M, Hernandez JM, Hossfeld DK, et al. The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood* 1999;93: 3601-9.

107. Akagi T, Motegi M, Tamura A, Suzuki R, Hosokawa Y, Suzuki H, et al. A novel gene, MALT1 at 18q21, is involved in t(11;18) (q21;q21) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Oncogene* 1999;18: 5785-94.
108. Morgan JA, Yin Y, Borowsky AD, Kuo F, Nourmand N, Koontz JI, et al. Breakpoints of the t(11;18)(q21;q21) in mucosa-associated lymphoid tissue (MALT) lymphoma lie within or near the previously undescribed gene MALT1 in chromosome 18. *Cancer Res* 1999;59: 6205-13.
109. Lucas PC, Kuffa P, Gu S, Kohrt D, Kim DS, Siu K, et al. A dual role for the API2 moiety in API2-MALT1-dependent NF-kappaB activation: heterotypic oligomerization and TRAF2 recruitment. *Oncogene* 2007;26: 5643-54.
110. Zhou H, Du MQ, Dixit VM. Constitutive NF-kappaB activation by the t(11;18)(q21;q21) product in MALT lymphoma is linked to deregulated ubiquitin ligase activity. *Cancer Cell* 2005;7: 425-31.
111. Staal J, Driège Y, Bekaert T, Demeyer A, Muyllaert D, Van Damme P, et al. T-cell receptor-induced JNK activation requires proteolytic inactivation of CYLD by MALT1. *EMBO J* 2011;30: 1742-52.
112. Hosokawa Y, Suzuki H, Nakagawa M, Lee TH, Seto M. API2-MALT1 fusion protein induces transcriptional activation of the API2 gene through NF-kappaB binding elements: evidence for a positive feed-back loop pathway resulting in unremitting NF-kappaB activation. *Biochem Biophys Res Commun* 2005;334: 51-60.
113. Baens M, Fevery S, Sagaert X, Noels H, Hagens S, Broeckx V, et al. Selective expansion of marginal zone B cells in Emicro-API2-MALT1 mice is linked to enhanced IkappaB kinase gamma polyubiquitination. *Cancer Res* 2006;66: 5270-7.
114. Rosebeck S, Madden L, Jin X, Gu S, Apel IJ, Appert A, et al. Cleavage of NIK by the API2-MALT1 fusion oncoprotein leads to noncanonical NF-kappaB activation. *Science* 2011;331: 468-72.
115. Nie Z, Du MQ, McAllister-Lucas LM, Lucas PC, Bailey NG, Hogaboam CM, et al. Conversion of the LIMA1 tumour suppressor into an oncogenic LMO-like protein by API2-MALT1 in MALT lymphoma. *Nat Commun* 2015;6: 5908.
116. Chanudet E, Ye H, Ferry J, Bacon CM, Adam P, Muller-Hermelink HK, et al. A20 deletion is associated with copy number gain at the TNFA/B/C locus and occurs preferentially in translocation-negative MALT lymphoma of the ocular adnexa and salivary glands. *J Pathol* 2009;217: 420-30.
117. Kim WS, Honma K, Karnan S, Tagawa H, Kim YD, Oh YL, et al. Genome-wide array-based comparative genomic hybridization of ocular marginal zone B cell lymphoma: comparison with pulmonary and nodal marginal zone B cell lymphoma. *Genes Chromosomes Cancer* 2007;46: 776-83.
118. Honma K, Tsuzuki S, Nakagawa M, Karnan S, Aizawa Y, Kim WS, et al. TNFAIP3 is the target gene of chromosome band 6q23.3-q24.1 loss in ocular adnexal marginal zone B cell lymphoma. *Genes Chromosomes Cancer* 2008;47: 1-7.
119. Chanudet E, Huang Y, Ichimura K, Dong G, Hamoudi RA, Radford J, et al. A20 is targeted by promoter methylation, deletion and inactivating mutation in MALT lymphoma. *Leukemia* 2010;24: 483-7.
120. Honma K, Tsuzuki S, Nakagawa M, Tagawa H, Nakamura S, Morishima Y, et al. TNFAIP3/A20 functions as a novel tumor suppressor gene in several subtypes of non-Hodgkin lymphomas. *Blood* 2009;114: 2467-75.

121. Novak U, Rinaldi A, Kwee I, Nandula SV, Rancoita PM, Compagno M, et al. The NF- κ B negative regulator TNFAIP3 (A20) is inactivated by somatic mutations and genomic deletions in marginal zone lymphomas. *Blood* 2009;113: 4918-21.
122. Kato M, Sanada M, Kato I, Sato Y, Takita J, Takeuchi K, et al. Frequent inactivation of A20 in B-cell lymphomas. *Nature* 2009;459: 712-6.
123. Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. *Nature* 2009;459: 717-21.
124. Schmitz R, Hansmann ML, Bohle V, Martin-Subero JI, Hartmann S, Mechtersheimer G, et al. TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma. *J Exp Med* 2009;206: 981-9.
125. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature* 2011;470: 115-9.
126. Li ZM, Rinaldi A, Cavalli A, Mensah AA, Ponzoni M, Gascoyne RD, et al. MYD88 somatic mutations in MALT lymphomas. *Br J Haematol* 2012;158: 662-4.
127. Yan Q, Wang M, Moody S, Xue X, Huang Y, Bi Y, et al. Distinct involvement of NF-kappaB regulators by somatic mutation in ocular adnexal malt lymphoma. *Br J Haematol* 2013;160: 851-4.
128. Moody S, Escudero-Ibarz L, Wang M, Xue W, Zeng N, Brugiatielli Met al. Distinct mutation profile of MALT lymphoma compared to otehr B-cell lymphoma characterised by NF-kB activation. 17th meeting of the European Association for Haematopathology; 2014;PP-Lymph-002.
129. Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med* 2012;367: 826-33.
130. Liu F, Karube K, Kato H, Arita K, Yoshida N, Yamamoto K, et al. Mutation analysis of NF-kappaB signal pathway-related genes in ocular MALT lymphoma. *Int J Clin Exp Pathol* 2012;5: 436-41.
131. Gachard N, Parrens M, Soubeyran I, Petit B, Marfak A, Rizzo D, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. *Leukemia* 2013;27: 183-9.
132. Zhu D, Ikpat OF, Dubovy SR, Lossos C, Natkunam Y, Chapman-Fredricks JR, et al. Molecular and genomic aberrations in Chlamydophila psittaci negative ocular adnexal marginal zone lymphomas. *Am J Hematol* 2013;88: 730-5.
133. Streubel B, Vinatzer U, Lamprecht A, Raderer M, Chott A. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. *Leukemia* 2005;19: 652-8.
134. Wlodarska I, Veyt E, De Paepe P, Vandenberghe P, Nooijen P, Theate I, et al. FOXP1, a gene highly expressed in a subset of diffuse large B-cell lymphoma, is recurrently targeted by genomic aberrations. *Leukemia* 2005;19: 1299-305.
135. Fenton JA, Schuurin E, Barrans SL, Banham AH, Rollinson SJ, Morgan GJ, et al. t(3;14)(p14;q32) results in aberrant expression of FOXP1 in a case of diffuse large B-cell lymphoma. *Genes Chromosomes Cancer* 2006;45: 164-8.

136. Vinatzer U, Gollinger M, Mullauer L, Raderer M, Chott A, Streubel B. Mucosa-associated lymphoid tissue lymphoma: novel translocations including rearrangements of ODZ2, JMJD2C, and CNN3. *Clin Cancer Res* 2008;14: 6426-31.
137. Ansell SM, Akasaka T, McPhail E, Manske M, Braggio E, Price-Troska T, et al. t(X;14)(p11;q32) in MALT lymphoma involving GPR34 reveals a role for GPR34 in tumor cell growth. *Blood* 2012;120: 3949-57.
138. Baens M, Finalet FJ, Tousseyn T, Urbankova H, Michaux L, de Leval L, et al. t(X;14)(p11.4;q32.33) is recurrent in marginal zone lymphoma and up-regulates GPR34. *Haematologica* 2012;97: 184-8.
139. Hovelmeyer N, Reissig S, Xuan NT, Adams-Quack P, Lukas D, Nikolaev A, et al. A20 deficiency in B cells enhances B-cell proliferation and results in the development of autoantibodies. *Eur J Immunol* 2011;41: 595-601.
140. Sagaert X, Theys T, Wolf-Peeters C, Marynen P, Baens M. Splenic marginal zone lymphoma-like features in API2-MALT1 transgenic mice that are exposed to antigenic stimulation. *Haematologica* 2006;91: 1693-6.
141. Cerutti A, Cols M, Puga I. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. *Nat Rev Immunol* 2013;13: 118-32.
142. Magri G, Miyajima M, Bascones S, Mortha A, Puga I, Cassis L, et al. Innate lymphoid cells integrate stromal and immunological signals to enhance antibody production by splenic marginal zone B cells. *Nat Immunol* 2014;15: 354-64.
143. Cerutti A, Puga I, Cols M. New helping friends for B cells. *Eur J Immunol* 2012;42: 1956-68.
144. Eberl G, Colonna M, Di Santo JP, McKenzie AN. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology. *Science* 2015;348: aaa6566.
145. Liu H, Ye H, Ruskone-Fourmestraux A, de Jong D, Pileri S, Thiede C, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. *Gastroenterology* 2002;122: 1286-94.
146. Goatly A, Bacon CM, Nakamura S, Ye H, Kim I, Brown PJ, et al. FOXP1 abnormalities in lymphoma: translocation breakpoint mapping reveals insights into deregulated transcriptional control. *Mod Pathol* 2008;21: 902-11.
147. Bi Y, Zeng N, Chanudet E, Huang Y, Hamoudi RA, Liu H, et al. A20 inactivation in ocular adnexal MALT lymphoma. *Haematologica* 2012;97: 926-30.
148. Du MQ. MALT lymphoma: many roads lead to nuclear factor-kappab activation. *Histopathology* 2011;58: 26-38.
149. Du M.Q. Genetics and molecular pathogenesis of marginal zone lymphoma. *In* G. Lenz and L. Pasqualucci (eds.), *Malignant Lymphomas.*, pp. 101-126. Berlin: De Gruyter, 2016.

FIGURE LEGENDS:

Figure 1: NF- κ B activation pathways and their major regulators. The signalling from the TNFR1, TLR, IL-1R, and antigen receptor (BCR) activates the canonical NF- κ B pathway, which is characterised by activation of the IKK complex, phosphorylation and degradation of I κ B. The signalling from CD40, BAFFR and LT β R activates the non-canonical NF- κ B pathway, which is featured by activation of NIK, proteolytic processing of p100 and generation of functional active p52. The canonical NF- κ B pathway is negatively regulated by A20 (TNFAIP3), a target of NF- κ B, while the non-canonical pathway is negatively controlled by TRAF3. The regulators that are activated by genetic changes in MALT lymphoma are highlighted by a red colour circle, while those that are inactivated by genetic changes are highlighted by a black colour circle. Modified with permission from Du MQ, Histopathology 2011 [148].

TNFR: tumour necrosis factor receptor; TLR: toll like receptor; IL-1R: interleukin 1 receptor; BCR: B-cell receptor; TCR: T-cell receptor; TRAF: TNF associated factor; RIP1: receptor interacting protein 1; TAK1: transforming growth factor β activating kinase; TAB: TAK binding protein; IKK: inhibitor of NF- κ B kinase; NEMO: NF- κ B essential modulator; I κ B: inhibitor of NF- κ B; BAFFR: B cell activating factor receptor; LT β R: lymphotoxin β receptor; NIK: NF- κ B inducing kinase. K63Ub: K63 linked ubiquitin chain; K48Ub: K48 linked ubiquitin chain.

Figure 2: Multistage development of MALT lymphoma.

Figure 3: Frequencies of genetic abnormalities in MALT lymphoma of different sites. The data are based on our previous studies [79,90,116,119,145-147].

Figure 4: Key features of MALT lymphoma associated oncogenes or tumour suppresser genes.

T(1;14)(p22;q32)/*BCL10-IGH* and t(14;18)(q32;q21)/*IGH-MALT1* cause over-expression of BCL10 and MALT1 respectively, while t(11;18)(q21;q21)/*BIRC3(API2)-MALT1* fuses the N-terminal API2 to the C-terminal MALT1 and generates a chimeric fusion product. Various breakpoints in API2 and MALT1 and their frequencies are indicated. *TNFAIP3 (A20)* is commonly inactivated by deleterious mutations and deletion. Modified with permission from [127,148].

Figure 5: The proposed model of molecular pathogenesis of gastric MALT lymphoma with and without chromosome translocation.

The oncogenic products of t(1;14)(p22;q32)/*BCL10-IGH*, t(14;18)(q32;21)/*IGH-MALT1* and t(11;18)(q21;q21)/*API2-MALT1* activate the canonical NF- κ B pathway. They may further augment their mediated NF- κ B activation by enhancing expression of surface receptors TLR6 and CCR2, as well as proteolytic cleavage of the negative inhibitor TNFAIP3/A20. In addition, the API2-MALT1 fusion product gains ability to cleave NIK and generate a stable NIK C-terminal fragment, capable of activating the non-canonical NF- κ B pathway, and also to cleave LIMA1 and generate a LIM domain-only (LMO) fragment, conferring oncogenic properties. Over-expression of BCL10 or MALT1 may also indirectly enhance non-canonical NF- κ B signalling via BAFFR. These genetic changes may potentially cooperate with the signalling from BCR, BAFFR and CD40, together causing constitutive activation of both canonical and non-canonical NF- κ B pathways.

The growth of translocation negative MALT lymphoma is largely driven by *H. pylori* generated immune responses including signalling from CD40 and CD86 through bystander T-cell helps, and direct triggering of TLR and BCR by *H. pylori* associated lipopolysaccharides and autoantigen respectively. This explains that most of translocation negative gastric MALT lymphomas are responsive to *H. pylori* eradication. Reproduced with permission from [148,149].

TLR: toll like receptor; BCR: B-cell receptor; MAPK: MAP kinase; I κ B: inhibitor of NF- κ B; BAFFR: B cell activating factor receptor; K48Ub: K48 linked ubiquitin chain. NIK: NF- κ B inducible kinase; LIMA1: LIM domain and actin-binding protein 1.

Table 1: Examples of biased IG gene usage in MALT lymphoma of different anatomic sites.

Sites of MALT lymphoma	Aetiology	Biased IG gene usage#	References
Stomach	<i>Helicobacter pylori</i>	IGHV3-7 IGHV1-69 IGHV1-2 (?) IGHV3-23 (?)	[42,45-49]
Ocular adnexa	<i>Chlamydia psittaci</i>	IGHV4-34/IGKV3-20* (~12%) IGHV3-7 (?) IGHV3-23 (?) IGHV3-30 (?)	[44,50-54]
Salivary glands	lymphoepithelial sialadenitis	IGHV1-69/IGKV3-20 (~50%)	[42,55,56]
Thyroid	Hashimoto thyroiditis	IGHV3-30 (?)	[57]
Skin	<i>Borrelia burgdorferi</i>	IGHV3-30 (?) IGHV1-69 (?)	[58-60]
Lung	<i>Achromobacter xylosoxidans</i>	IGHV4-34 (?)	[61]

#where a IGHV member might be biased used, but not yet investigated extensively, is indicated by a question mark;

*frequently in *Chlamydia psittaci* negative cases.

Table 2: Properties of IG gene rearrangements and their encoded BCR in MALT lymphoma.

IG genes bias-used in MALT lymphoma	Known genetic features of IG rearrangement	Known IG properties	References
IGHV1-69	<ul style="list-style-type: none"> – short CDR3 sequence frequently with high homology to those of rheumatoid factor; – variable mutations in IGHV with few intraclonal variations; 	rheumatoid factors, self-polyreactive	[42,48,54,56]
IGHV3-7	<ul style="list-style-type: none"> – CDR3 sequence frequently with high homology to those of rheumatoid factor; 	rheumatoid factors, self-polyreactive	[42,48,54]
IGHV3-23/IGKV3-20	n/a	self-polyreactive	[43]
IGHV3-30 /IGKV1-33	n/a	self-polyreactive	[43]
IGHV4-34/ IGKV3-20*	<ul style="list-style-type: none"> – Contains unique and conserved FR1 motif (Q⁶W⁷ and A²⁴V²⁵Y²⁶) 	Binding to <i>N</i> -acetyl-lactosamine residues; polyreactive	[43,64,65]

n/a: not available yet

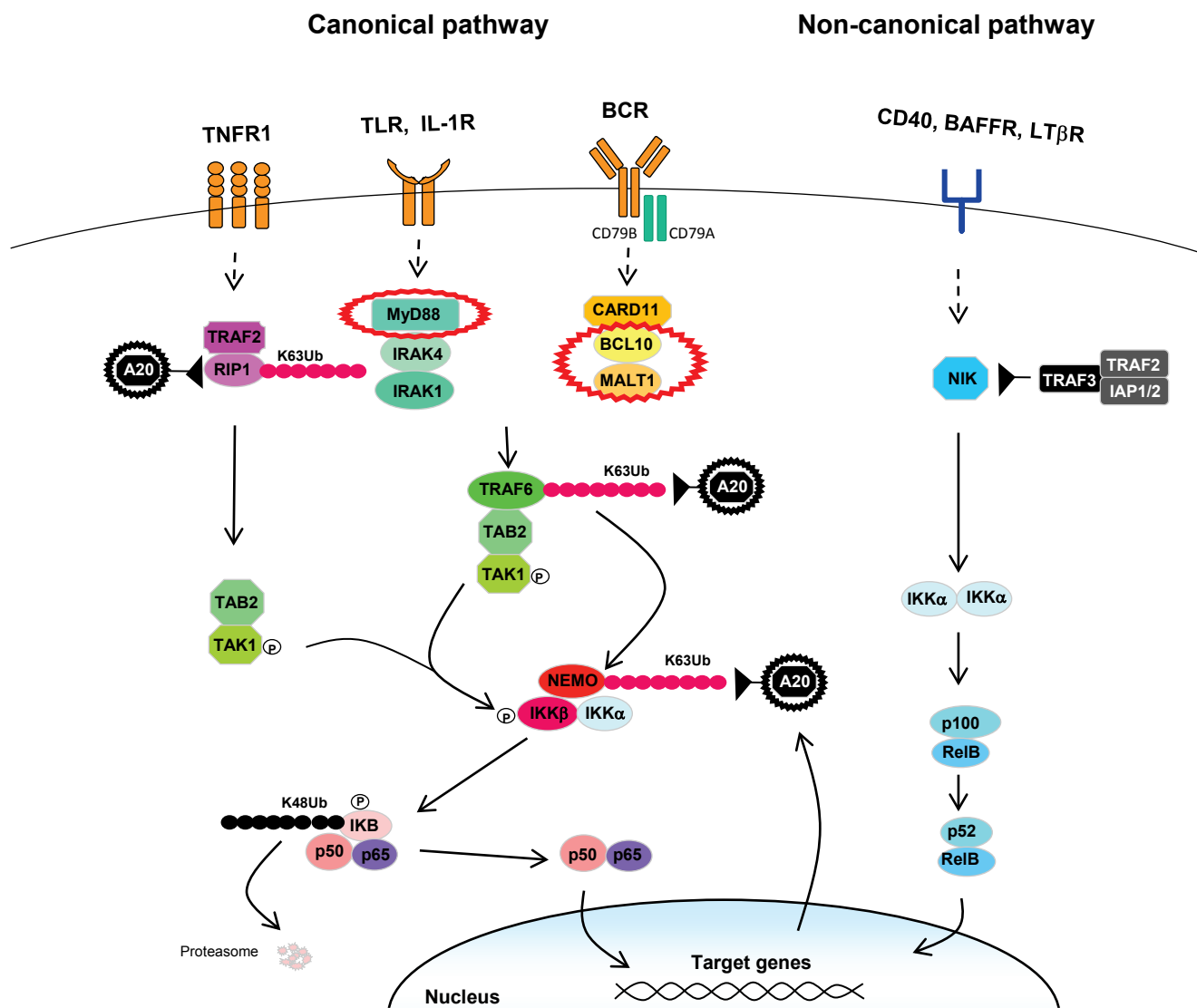


Figure 1. NF-κB activation pathways and their major regulators.

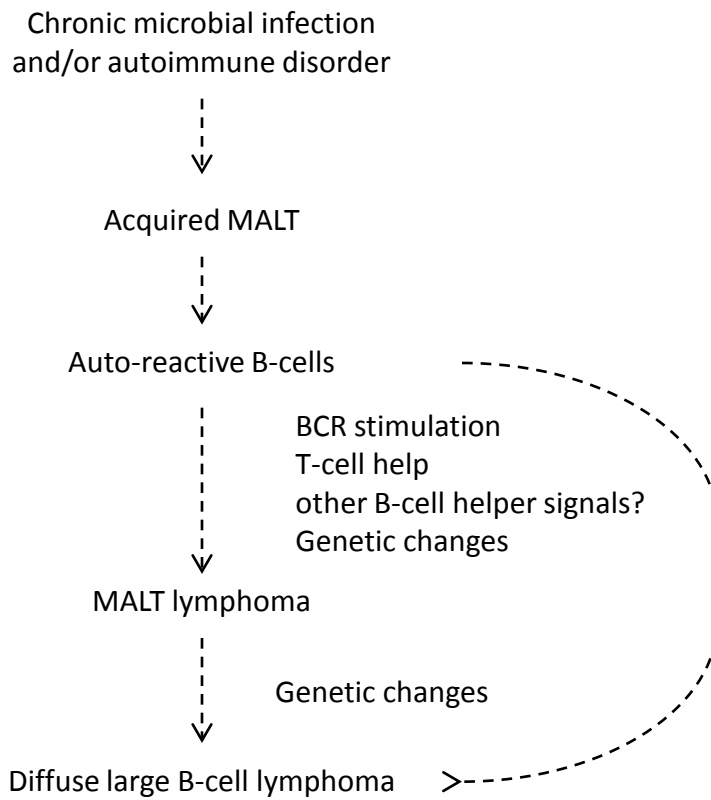


Figure 2: Multistage development of MALT lymphoma.

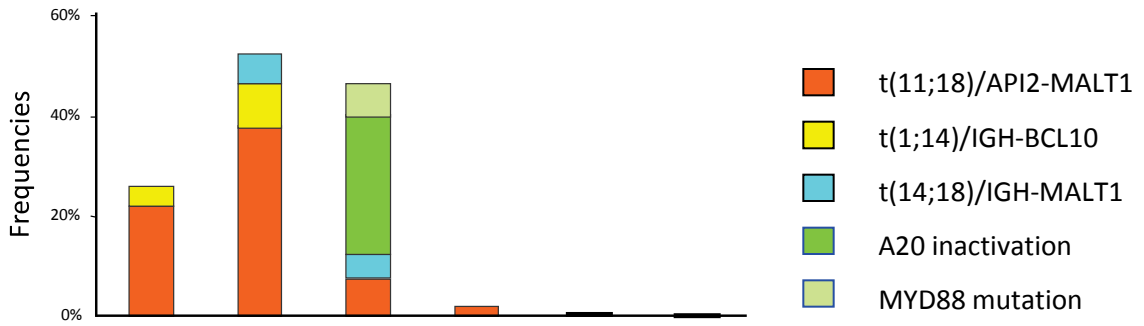


Figure 3: Frequencies of genetic abnormalities in MALT lymphoma of different sites.

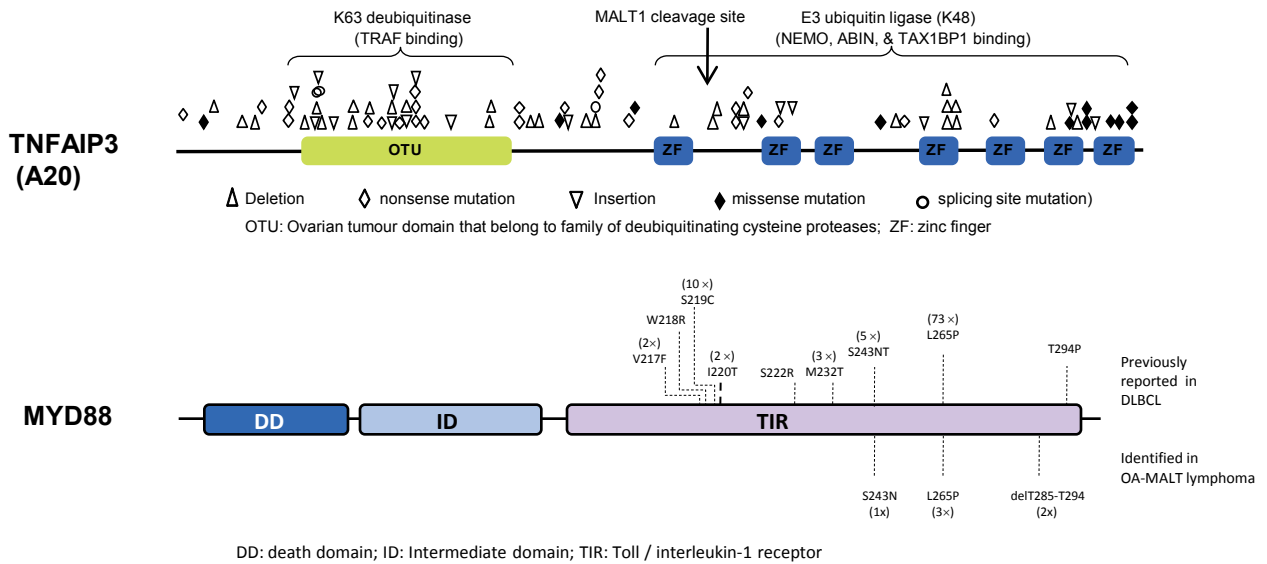
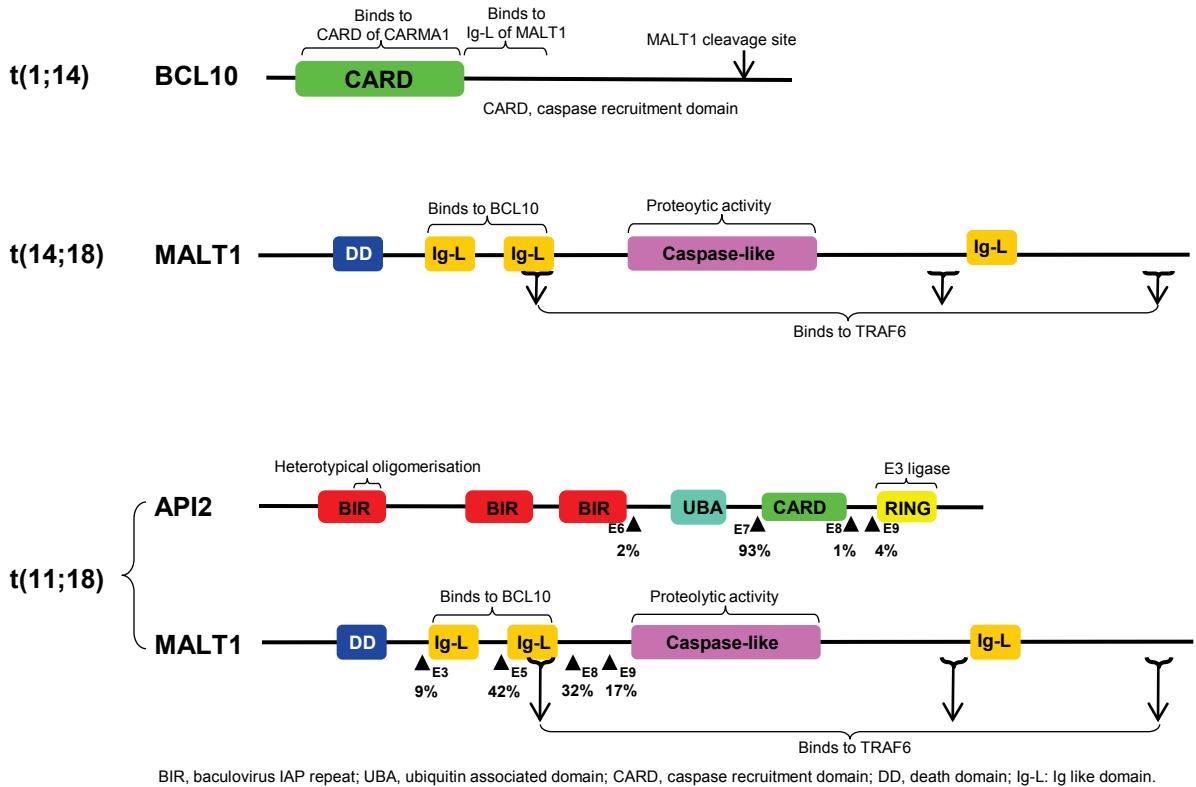


Figure 4: Key features of MALT lymphoma associated oncogenes or tumour suppresser genes.

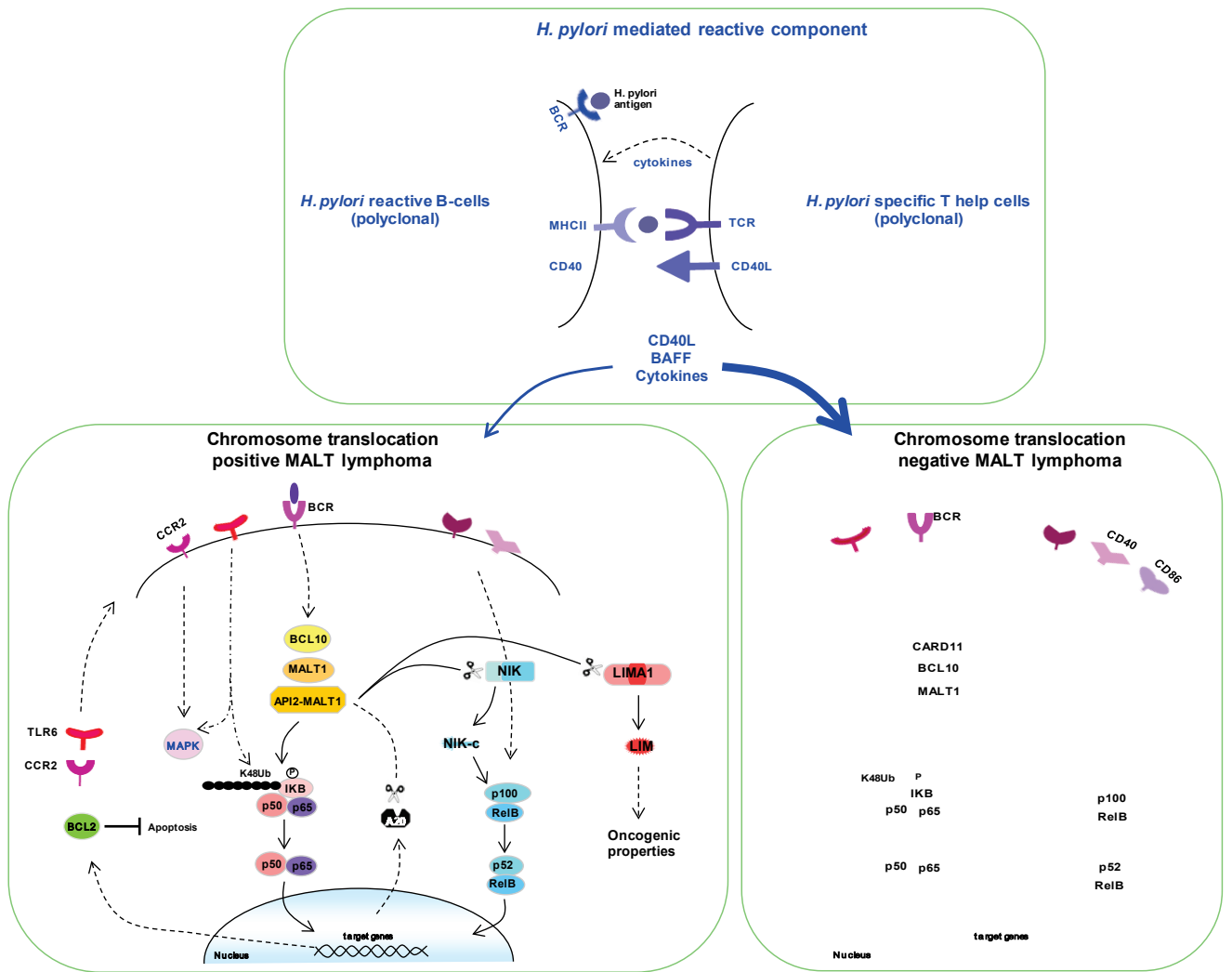


Figure 5: The proposed model of molecular pathogenesis of gastric MALT lymphoma with and without chromosome translocation.